Lilly

Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

April 15, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: [Docket No. 99D-0121] Guidance for Industry; Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System

Dear Madam or Sir:

Eli Lilly and Company is pleased to have the opportunity to provide comments on the draft guidance for industry, Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System.

We commend the FDA for a scientifically based approach to providing for waivers of *in vivo* bioavailability and bioequivalence studies as described in the draft guidance. Attached please find our comments on the draft guidance. We hope that these comments will result in revisions that further enhance the positive impact of this guidance.

Please feel free to contact me at 317-276-4509 for clarification of any comments.

Sincerely,

ELI LILLY AND COMPANY

David J. Miner, Ph.D.
Director, US Regulatory Affairs
(CMC - Marketed Products)

DJM:at

Enclosure

99D-0121

C 8

Re: [Docket No. 99D-0121] Guidance for Industry; Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System

Eli Lilly and Company applauds the efforts which the FDA has expended to develop the waiver of *in vivo* bioavailability and bioequivalence studies draft guidance document. This document represents a significant improvement in the process for addressing this issue. We also appreciate the opportunity to comment on the document.

Eli Lilly and Company has three comments concerning the draft guidance as follows:

Comment Re Draft Guidance Section IV.B.2.

IV. Methodology for Classifying a Drug
  B. Determining Solubility Class
    2. Intestinal Permeability Methods (Page 5)

Eli Lilly and Company proposes adding an alternative procedure for the determination of permeability values via *in vitro* drug transport experiments across a monolayer of cultured human intestinal cells.

The bottom paragraph on page 5 of the draft guidance details the use of internal standards run as a mixture with the test compound whose permeability is being evaluated. For the following reasons, we propose the additional alternative of adding internal standards *at the end* of the test compound drug transport experiment and measuring internal standard *percent transported* values rather than permeability values:

1. The possibility of internal standard interference with the test compound permeability measurements is eliminated. No pre-evaluation of compatibility with the test compound is necessary. In our laboratories, sulforhodamine 101, a known low permeability paracellular leakage marker, has been routinely added as an "end" standard to the donor chamber *after* the test compound drug transport experiment has been completed. Measurement of this marker and comparison to a previously established threshold value of monolayer integrity (<0.2% transported in 30 minutes) affords an indication of barrier integrity during the previously run drug transport experiment. Similarly, a representative high permeability internal standard could be evaluated.

2. Establishing threshold values and/or specification ranges for representative "end" standards based on their *percent transported* values is desirable and scientifically efficient for two reasons: unlike permeability determinations, standard curves are not needed and fewer donor and receiver total samplings are required. Instead of three

standard curves (one each for low and high internal standard and one for the test compound) only one would need to be prepared.

Additionally, we typically take nine samplings (three initial donors, four receivers, two final donors) to calculate a quality permeability value. Percent transported data provides a savings of seven samplings since only one donor and one receiver need be taken.

The draft guidance suggests that once the correlation between permeability and extent-of absorption data in humans has been established with 20 or more model compounds, determining the permeability of a judiciously selected high standard can serve as the threshold for assigning BCS "high permeability". If percent transported rather than permeability values are obtained for both the low and high standards, these data give evidence of the reproducibility of the experimental method for that particular investigation. Biopharmaceutical classification based upon test compound permeability is then extrapolated from the previously determined and validated model compound permeability *vs.* extent-of-absorption in human data.

Comment Re Draft Guidance Section V.3.

V. Requesting a Waiver of *In Vitro* BA/BE Studies
   3. "For waiver of an *in vivo* BA study.... When both the test and the reference products dissolve 85% or more of the label amount in $\leq$15 minutes, in all three dissolution media recommended above, a profile comparison is unnecessary." (Page 6)

As defined in this proposed guidance, an IR dosage form is considered rapidly dissolving when not less than 85% of the label amount of drug substance dissolves **within 30 minutes** in each of the three recommended media. Additionally, in a recent publication[1] by Kaus et al., the authors suggested that the criterion of 85% dissolution time in 15 minutes for classifying a rapidly dissolving drug product is relatively conservative. Their simulations over a range of permutations for gastric emptying times, intestinal transit times, dissolution rates, and effective permeabilities indicated that the pharmacokinetic parameters of C_{max} and AUC ratios exceeded 0.8 for values of T85% out to 1 hour.

Thus, dissolution test results of ≥85% dissolved in 30 minutes (rather than 15 minutes) for the test and reference product should not require profile testing via the f_2 metric. It is our opinion, based on the definition for "rapidly dissolving" provided in the draft guidance and physiological considerations, that this is a more appropriate guideline.

Comment Re Draft Guidance Section VI.A.

VI. Additional Considerations When Planning a Request For a Waiver
A. Instability in the Gastrointestinal Tract (Page 7)

In response to the draft guidance proposal that:

> "Stability in gastrointestinal fluids can be documented by (1) pH-stability profiles in the pH range of 1-8 **AND** (2) stability in gastric and intestinal fluids obtained from human subjects or animals. Drug solutions in these fluids can be incubated at 37°C for about three hours and analyzed using a validated stability indicating assay. Significant degradation or loss (>5%) of a drug in about three hours could suggest potential instability.",

Eli Lilly and Company suggests that the above draft requirement (1) **AND** (2) be changed to (1) **OR** (2) for the following reasons:

1. It is our opinion that the collection of gastric fluids from humans or animals is neither practical or sufficiently standardized to allow the gathering of consistent data.

2. Use of biological gastric fluids for analytical testing would require further regulation or guidance on the collection, storage, and transportation practices associated with the handling of these fluids.

3. Use of these biological fluids would increase the complexity of analytical method validation.

4. We would suggest using a combination of standardized simulated gastric (USP) or intestinal fluid(s) (USP) for *in vitro* testing. The inherent inter and intra species variability between physical and chemical properties of biological fluids, collected from human or animal subjects, will be minimized or eliminated with the adoption of standardized compositions which can be prepared as needed.

   Alternately, it may be appropriate to use the simulated fluids referenced in a recent review[2]. The composition of gastric and intestinal media for both the fed and fasted state are provided. They are prepared using appropriate salts, surfactants, and at the appropriate pH, buffering capacity, and osmolarity.

5. We are opposed to increasing the incidence of invasive collection procedures to obtain these biological fluids at a time when the absolute correlation between *in vivo* and *in vitro* results in these actual fluids has not been established.

[1]"The Effect of In Vivo Dissolution, Gastric Emptying Rate, and Intestinal Transit Time of the Peak Concentration and Area-Under-the-Curve of Drugs with Different Gastrointestinal Permeabilities," Kaus, Gillespie, Hussain, Amidon, Pharmaceutical Research, Vol. 16, No. 2, 1999.

[2]"Dissolution Testing as a Prognostic Tool for Oral Drug Absorption: Immediate Release Dosage Forms," Dressman, Amidon, Reppas, Shah, Pharmaceutical Research, Vol. 15, No. 1, 1998.